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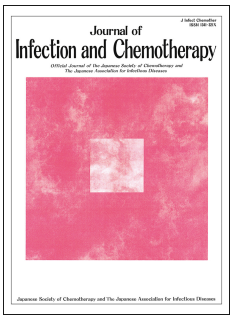

Ivermectin administration is associated with lower gastrointestinal complications and greater ventilator-free days in ventilated patients with COVID-19: A propensity score analysis

Kentaro Shimizu, Haruhiko Hirata, Daijiro Kabata, Natsuko Tokuhira, Moe Koide, Akiko Ueda, Jotaro Tachino, Ayumi Shintani, Akinori Uchiyama, Yuji Fujino, Hiroshi Ogura

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(Title Page)

1) Title

Ivermectin administration is associated with lower gastrointestinal complications and greater ventilator-free days in ventilated patients with COVID-19: A propensity score analysis

2) Author names and affiliations

(Authors)

Kentaro Shimizu[1], shimiken@hp-emerg.med.osaka-u.ac.jp

Haruhiko Hirata[2], charhirata@imed3.med.osaka-u.ac.jp

Daijiro Kabata[3], kabata.daijiro@med.osaka-cu.ac.jp

Natsuko Tokuhira[4], tokuhira@hosp.med.osaka-u.ac.jp

Moe Koide[4], koide@hosp.med.osaka-u.ac.jp

Akiko Ueda[5], aueda@hp-lab.med.osaka-u.ac.jp

Jotaro Tachino[1], jotarotachino@hp-emerg.med.osaka-u.ac.jp

Ayumi Shintani, ayumi.shintani@gmail.com

Akinori Uchiyama[4], auchiyama@hp-icu.med.osaka-u.ac.jp

Yuji Fujino[4], fujino@anes.med.osaka-u.ac.jp

Hiroshi Ogura[1], ogura@hp-emerg.med.osaka-u.ac.jp

(Affiliations)

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[1]Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

[2]Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University

2-2 Yamadaoka, Suita 565-0871, Japan

[3]Department of Medical Statistics, Osaka City University Graduate School of Medicine, 1-4-3, Asahimachi, Abeno-ku, Osaka, 545-0051, Japan

[4]Intensive Care Unit, Osaka University Hospital, Osaka University, Japan

2-15 Yamadaoka, Suita, Osaka 565-0871, Japan

[5]Laboratory for Clinical Investigation, Osaka University Hospital, Osaka University, Japan

2-15 Yamadaoka, Suita, Osaka 565-0871, Japan

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3) Corresponding author:

Kentaro Shimizu, M.D.

Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita-city, Osaka 565-0871, Japan

Telephone (fax): 81-6-6879-5707(5720)

E-mail: shimiken@hp-emerg.med.osaka-u.ac.jp

4) Authorship statement

SK, NT, and MK reviewed the record and drafted the manuscript. HH and AU confirmed the clinical record as clinical attendants. DK, TJ and AS reviewed statistical parts and clinical application. YF and OH contributed to the discussion and managed this research. All authors read the draft and revised it critically and approved the final manuscript. All authors meet the ICMJE authorship criteria.

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Abstract

Introduction: COVID-19 patients have been reported to have digestive symptoms with poor outcome. Ivermectin, an antiparasitic drug, has been used in COVID-19 patients. The objective of this study was to evaluate whether ivermectin has effects on gastrointestinal complications and ventilator-free days in ventilated patients with COVID-19.

Methods: COVID-19 patients who were mechanically ventilated in the ICU were included in this study. The ventilated patients who received ivermectin within 3 days after admission were assigned to the Ivermectin group, and the others were assigned to the Control group. Patients in the Ivermectin group received ivermectin 200 μg/kg via nasal tube. The incidence of gastrointestinal complications and ventilator-free days within 4 weeks from admission were evaluated as clinical outcomes using a propensity score with the inverse probability weighting method.

Results: We included 88 patients in this study, of whom 39 patients were classified into the Ivermectin group, and 49 patients were classified into the Control group. The hazard ratio for gastrointestinal complications in the Ivermectin group as compared with the Control group was 0.221 (95% confidence interval [CI], 0.057 to 0.855; $p = 0.029$) in a Cox proportional-hazard regression model. The odds ratio for ventilator-free days as compared with the Control group was 1.920 (95% CI, 1.076 to 3.425; $p = 0.027$) in a proportional odds logistic regression model.

Conclusions: Ivermectin improved gastrointestinal complications and the number of ventilator-free days in severe COVID-19 patients undergoing mechanical ventilation. Prevention of gastrointestinal

symptoms by SARS-Cov-2 might be associated with COVID-19 outcome.

Keywords:

COVID-19, ivermectin, intensive care unit, ventilated, diarrhea, gastrointestinal, ventilator-free days

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) pandemic is an emergency situation throughout the world. As treatment, dexamethasone has been used as an effective anti-inflammatory drug [1], but dexamethasone weakens host immunity [2]. Remdesivir, an antiviral drug, is a nucleoside analogue prodrug used for various viral infections and decreases the time to clinical improvement in adults with severe COVID-19 [3]. However, there are limited data in patients with mechanical ventilation [4].

Ivermectin is a drug that has been used to treat parasitic infections such as onchocerciasis and lymphatic filariasis throughout the world for more than 30 years, with more than 3.7 billion doses dispensed in Africa and Central and South America to control tropical diseases [5]. Ivermectin shows in vitro activity against a broad range of viruses, including not only HIV, dengue, influenza, and Zika virus but also SARS-CoV-2 [6]. Clinical research by Rajter et al. [7] found that ivermectin treatment was associated with lower mortality in 280 COVID-19 patients in a propensity score-matching study. Contrastingly, in a randomized clinical trial of 400 patients with mild COVID-19, ivermectin administration did not decrease the time to resolution of symptoms within 21 days [8]. Thus, the effects of ivermectin are controversial, and there are few clinical data on intubated COVID-19 patients in the intensive care unit (ICU).

COVID-19 causes gastrointestinal (GI) symptoms such as nausea or vomiting, diarrhea, and loss of

appetite as reported in a systemic review of 6686 patients [9]. There is little research on established treatment for these GI symptoms [10]. As we have been struggling against refractory diarrhea and regurgitation in our patients with COVID-19, we planned to use an antiviral oral drug for intestinal prophylaxis, and we selected ivermectin as the drug. Therefore, the objective of this study was to evaluate whether ivermectin improved GI complications and respiratory conditions in mechanically ventilated patients with COVID-19.

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Methods

Patients

Patients who were more than 20 years old, were placed on a ventilator within 3 days after admission to the ICU, and were diagnosed as having COVID-19 in the Department of Traumatology and Acute Critical Medicine and Intensive Care Unit, Osaka University Hospital during the period December 2020 to May 2021 were eligible for enrollment in this retrospective study [11]. The emergency medical system in our country has three designated levels according to the perceived acuity of the patients. Our designated tertiary hospital deals with patients who need to be managed in the operating room or the ICU [12]. During the study period, only severe COVID-19 patients who required a ventilator were transferred to our hospital.

Interventions

The use of ivermectin has been approved for strongyloidiasis and scabies (200 μg/kg per 2 weeks) in Japan. The off-label use for COVID-19 was approved in Osaka University Hospital from February 2021. The ventilated patients who provided informed consent for the use of ivermectin within 3 days after admission received ivermectin and were assigned to the Ivermectin group, and the patients who did not receive ivermectin within 3 days were assigned to the Control group. Patients in the Ivermectin group received ivermectin 200 μg/kg per 2 weeks via nasal tube. Antibiotics were administered under the same policy during the entire study period [13]. This study was approved by the institutional review board of Osaka University (approval no. 21163). Informed consent was obtained from the family of each patient.

Outcome variables

Diarrhea was defined as the acute onset of continuous loose or liquid stools occurring more than twice. Regurgitation was defined as reflux volume from the gastric tube of more than 300 mL/day. GI complications were defined as diarrhea or regurgitation. Ventilator-free days (VFD) were defined as the number of days alive and free of mechanical ventilation within 4 weeks from admission [14]. The primary outcome was VFD. The secondary outcomes included diarrhea, regurgitation, and GI complications within 4 weeks from admission.

Statistical analysis

All patient characteristics are summarized using medians with interquartile ranges (IQR) and proportions with counts for continuous variables and categorical variables, respectively. The differences in distributions of the covariates between the Ivermectin and Control groups were assessed using standardized mean differences (SMD).

We estimated the cumulative event-free probabilities of the first incidence of diarrhea, regurgitation, and GI complications using the Kaplan-Meier method. Then, we estimated the effect of ivermectin use on these events using Cox proportional-hazard regression models. Furthermore, we assessed the effect of ivermectin use on VFD and the number of ICU-free days within 28 days from ICU admission using proportional-odds logistic regression models. To reduce the biases that were introduced by the imbalances of the covariates' distributions between the groups, we used the inverse probability weighting (IPW) method. The probability of receiving ivermectin, which is referred to as the propensity score, was estimated by a multivariable logistic regression model considering the following covariates of age, sex, P/F ratio, extracorporeal membrane oxygenation, use of concomitant drugs (remdesivir, favipiravir, dexamethasone, and methylprednisolone), and comorbidities (hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease). To avoid variance inflation due to the extreme weights, which were introduced by the extremely high and low estimated propensity scores, we trimmed the propensity scores in the un-overlapped area of the propensity score distributions in both groups.

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All statistical inferences were made with a two-sided 5% significance level using R software (https://cran.r-project.org/).

Results

All of the patients tolerated ivermectin, and there were no clear adverse events in any patients. Patient characteristics are listed in Table 1.

The Ivermectin group contained 39 patients, and the Control group contained 49 patients. Patients in the Ivermectin group had significantly lower age and less chronic kidney disease than those in the Control group. To adjust for age, sex, respiratory condition, concomitant drugs, and comorbidities, we used propensity score via the IPW method. Most patients were intubated on admission, and median time from admission to intubation had no significant differences between the Ivermectin group (median 0, IQR -0.5–0 days) and Control group (median 0, IQR -1–0 days). There were no significant differences in blood test results except for that of serum creatinine (Table 2).

The frequencies of diarrhea, regurgitation, and GI complications in the Ivermectin group were significantly lower than those in the Control group. The intubation period was significantly lower and the number of VFD was significantly greater in the Ivermectin versus Control group (Table 3). The cumulative event-free probabilities of the first incidence of GI complications and extubation using the Kaplan-Meier method are shown in Fig. 1. The mortality within 28 days did not differ significantly between the groups, but the mortality in the whole ICU stay had significantly lower in the Ivermectin

group versus the Control group (0% vs. 16.3%; $p < 0.05$).

In a Cox proportional-hazard regression model, the hazard ratio for GI complications for the Ivermectin group as compared with the Control group was 0.221 (95% confidence interval [CI], 0.057 to 0.855; $p = 0.029$) after adjustment for covariates using propensity score with IPW method (Table 4)(Fig.2). In the proportional odds logistic regression model, the odds ratio for VFD as compared with the control group was 1.920 (95% CI, 1.076 to 3.425; $p = 0.027$) after using the same adjustment method.

Discussion

This study showed that the administration of ivermectin reduced the incidences of GI complications and increased VFD in patients with COVID-19 undergoing mechanical ventilation. Regarding clinical research, in a meta-analysis of 9 randomized controlled trials in 1788 COVID-19 patients, ivermectin was associated with decreased mortality [15]. However, these studies did not evaluate GI complications and VFD. In addition, most patients were not intubated when ivermectin was administered. We showed that even after patients worsened and required mechanical ventilation, administration of ivermectin via nasal tube could attenuate GI complications and shorten the duration of the intubation period.

Ivermectin has been shown to inhibit the viral replication of SARS-CoV-2 in vitro [16]. One of the presumed mechanisms is to be the inhibition of the enzyme importin α/β in the process of

translocation into the cell nucleus [6]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2). A deficiency in murine ACE2, which encodes a key regulatory enzyme of the renin-angiotensin system, results in highly increased susceptibility to diarrhea and intestinal inflammation induced by dextran sulfate sodium [17]. In a clinical study, fecal viral loads were detected [18], and digestive histologic and immunofluorescent staining revealed GI infection in patients with COVID-19 [19]. Previous reports showed that gastrointestinal complications occurred in about 15% of COVID-19 patients including mainly non-ventilated patients [10]. In the present study, 51.2% of COVID-19 ventilated patients in the Control group experienced GI complications. The ventilated patients had a higher prevalence of GI complications than the non-ventilated patients, so the effect modification of ivermectin could be expected to be different. It may be difficult to detect the effect of ivermectin in non-ventilated patients because of the smaller incidences of GI complications. These results suggest that ivermectin could reduce SARS-CoV-2 infection in the intestine and attenuate the symptoms of regurgitation and diarrhea.

Regarding with respiratory function, as the gut has been proposed as the ‘‘motor’’ of multiple organ failure [20], gut dysfunction is recognized as a causative factor in the progression of diseases such as sepsis, trauma, and infection. Intestinal injury by SARS-CoV-2 could cause intestinal inflammation and alteration of the gut microbiota, which might lead to progression of the respiratory disease seen with COVID-19. In the gut microbiota of COVID-19 patients, the diversity of normal gut microbiota bacteria is decreased and the number of opportunistic bacteria is increased [21, 22]. In the present

study, GI complications were significantly decreased in the Ivermectin group. It is reported that the approved dose of ivermectin does not result in an adequate serum concentration to treat COVID-19 [23]. Ivermectin could have a direct effect in the intestine, and prevention of SARS-CoV-2-related GI complications might also be associated with the increase in VFD seen in the present study. The mortality in the whole ICU stay had significantly lower in this research, and we need further randomized controlled study to demonstrate that.

Anti-inflammatory drugs are essential and effective, but dexamethasone, a glucocorticoid, affects immune cells [2] and is a double-edge sword, especially in aged patients with lowered immunity who have difficulty in upregulating immunity under steroid therapy. As a result, such patients with COVID-19 have been reported to suffer from fungal disease [24] and severe cytomegalovirus infection [25, 26]. It may be important to combine both an antiviral drug and an anti-inflammatory drug for SARS-COV-2 virus in the early stage of infection to prevent prolonged respiratory failure and reduce the accumulated dose of steroids. Ivermectin might be one of the promising antiviral drugs in the treatment of COVID-19.

This study has some limitations. An imbalance in the patients' age between the treatment groups remained after weighting. The mutant variants may be different with time, but we could not identify this. Additional well-designed studies are needed to provide further elucidation. Second, we propose that the intestinal effect of ivermectin might influence COVID-19 infection, and thus, evaluation of intestinal viral load could be a next target to confirm this supposition.

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Conclusions

The administration of ivermectin improved GI complications and VFD in ventilated patients with COVID-19. The beneficial influence of ivermectin on the intestines may improve outcome in these patients. Further research is needed to investigate the mechanism and effects of ivermectin treatment.

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Conflict of interest

The authors declare that they have no conflict of interests.

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Figure Legend

Fig. 1 The cumulative event-free probabilities of the first incidence of gastrointestinal complications (a) and extubation (b) using the Kaplan-Meier method

Fig. 2 The mean difference between treatment groups by inversed probability of weighting for propensity score analysis.

COPD; chronic obstructive pulmonary disease, ECMO; extracorporeal membrane oxygenation

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Table 1. Baseline patients' clinical and demographical characteristics

	[Original cohort]			[Weighted cohort]		
	Ivermectin	Control	SMD	Ivermectin	Control	SMD
N	39	49		70.78	74.36	
Age	60.00 [54.00, 64.50]	68.00 [58.00, 74.00]	0.807	60.00 [56.00, 67.00]	62.00 [55.64, 72.45]	0.417
Male	79.5 (31)	83.7 (41)	0.108	85.3 (60.3)	84.7 (63.0)	0.016
Respiratory condition						
P/F ratio	246.00 [173.00, 307.50]	236.00 [144.00, 344.00]	0.007	243.77 [144.07, 305.68]	226.45 [138.70, 334.04]	0.054
ECMO	7.7 (3)	8.2 (4)	0.017	9.7 (6.9)	9.0 (6.7)	0.024
Concomitant drugs						
Remdesivir	35.9 (14)	32.7 (16)	0.068	31.5 (22.3)	31.6 (23.5)	0.002
Favipiravir	28.2 (11)	36.7 (18)	0.183	39.6 (28.1)	37.4 (27.8)	0.045
Dexamethasone	100.0 (39)	100.0 (49)	<0.001	100.0 (70.8)	100.0 (74.4)	<0.001
Methylprednisolone	12.8 (5)	14.3 (7)	0.043	11.4 (8.1)	12.0 (8.9)	0.018
Comorbidities						
Hypertension	48.7 (19)	40.8 (20)	0.159	43.6 (30.8)	40.8 (30.3)	0.057
Hyperlipidemia	28.2 (11)	24.5 (12)	0.084	24.6 (17.4)	22.3 (16.6)	0.052
Diabetes mellitus	20.5 (8)	32.7 (16)	0.277	33.8 (23.9)	32.5 (24.2)	0.027
Hyperuricemia	17.9 (7)	8.2 (4)	0.294	11.6 (8.2)	6.9 (5.2)	0.161
Cardiovascular disease	15.4 (6)	10.2 (5)	0.156	17.7 (12.5)	9.9 (7.4)	0.225
COPD	5.1 (2)	10.2 (5)	0.192	2.8 (2.0)	6.7 (5.0)	0.184
Chronic kidney disease	0.0 (0)	14.3 (7)	0.577	0.0 (0.0)	9.4 (7.0)	0.456

Values are expressed as median [interquartile range] or percentage (frequency)

SMD; standardized mean difference, ECMO; extracorporeal membrane oxygenation, COPD; chronic obstructive pulmonary disease

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Table 2 Laboratory data on admission

	Units	Ivermectin	Control	*P* value
Hematology				
Red blood cells	$\times 10^4/\mu L$	457±11.0	438±9.6	0.207
Hemoglobin	g/dL	13.6±0.3	13.3±0.3	0.491
Hematocrit	%	39.7±0.9	39.0±0.7	0.565
White blood cells	/μL	9700±947	9500±828	0.840
Neutrophil	%	88.7±1.1	87.3±1.0	0.340
Lymphocyte	%	7.9±0.9	9.1±0.8	0.368
Monocyte	%	3.3±0.3	3.1±0.3	0.593
Eosinophil	%	0.1±0.0	0.1±0.0	0.335
Basophil	%	0.2±0.0	0.2±0.0	0.884
Platelets	$\times 10^4/\mu L$	21.2±12.9	18.5±11.3	0.119
Biochemistry				
Na	mEq/l	138±1.0	139±1.0	0.113
K	mEq/l	4.2±0.1	4.2±0.1	0.866
Cl	mEq/l	103±1.0	102±1.0	0.460
Urea nitrate	mg/dL	27±2.0	21±2.0	0.031
Uric acid	mg/dL	4.1±0.7	5.1±0.6	0.305
Creatinine	mg/dL	1.2±0.1	0.8±0.2	0.043
Calcium	mg/dL	8.3±0.1	8.3±0.1	0.693
Inorganic phosphate	mg/dL	3.4±0.3	3.6±0.2	0.444
Magnesium	mg/dL	2.2±0.1	2.2±0.0	0.940
AST	U/L	51±5.0	50±4.0	0.765
ALT	U/L	48±5.0	44±5.0	0.551
γGT	U/L	97±15	74±13	0.253
Alkaliphosphatase	U/L	74±6.0	74±6.0	0.997
Lactate dehydrogenase	U/L	511±37	516±32	0.922
Creatinine kinase	U/L	152±99	331±87	0.177
Amylase	U/L	90±21	94±19	0.893
Total bilirubin	mg/dL	0.6±0.2	0.6±0.3	0.781
C-reactive protein	mg/dL	9.2±1.0	9.4±0.9	0.908
Total protein	g/dL	6.2±0.1	6.3±0.1	0.849
Albumin	g/dL	2.7±0.1	2.7±0.1	0.687
Coagulation				
PT	%	79±2.0	74±3.0	0.215
PT-INR		1.2±0.0	1.3±0.1	0.110
APTT	%	40±4.0	45±4.1	0.387
Fibrinogen	mg/dL	478±22	519±25	0.230
D-dimer	μg/ml	21.8±6.1	6.7±7.0	0.106
FDP	ng/ml	47.5±14.5	13.5±16.2	0.121

AST; aspartate aminotransferase, ALT; alanine aminotransferase, γGT;γ-glutamyl transpeptidase
PT; prothrombin, APTT; activated partial thromboplastin time, FDP; fibrin/fibrinogen degradation

Table 3. Gastrointestinal complications and respiratory outcome

	Ivermectin (n=39)	Control (n=49)	*P* value
Diarrhea	10.3 (4)	38.8 (19)	0.003
Regurgitation	0 (0)	22.5 (11)	0.002
GI complications	10.3 (4)	51.2 (25)	<0.001
Intubation period	8 [6, 10]	13 [7, 38.5]	<0.001
Ventilator-free days	20 [18, 22]	15 [0, 21]	<0.001
ICU stay	10 [7, 13]	16 [8, 38.5]	<0.001
Death within 28 days	0 (0)	4.1 (2)	0.501

Values are expressed as percentage (frequency) or median [interquartile range]
GI; gastrointestinal

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Table 4. Analysis of the effects of ivermectin after adjusting for potential confounders

Variables	Effect measure	Effect	95% CI	*P* value
Diarrhea	Hazard ratio	0.378	0.098 - 1.451	0.156
Regurgitation	Hazard ratio	0.000	0.000 - 0.000	<0.001
GI complications	Hazard ratio	0.221	0.057 - 0.855	0.029
Ventilator-free days	Odds ratio	1.920	1.076 - 3.425	0.027
ICU-free days	Odds ratio	1.747	0.980 - 3.116	0.059
Mortality	Hazard ratio	0.001	0.000 - 0.005	<0.001

CI; confidence interval, GI; gastrointestinal

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Fig.1 (a)

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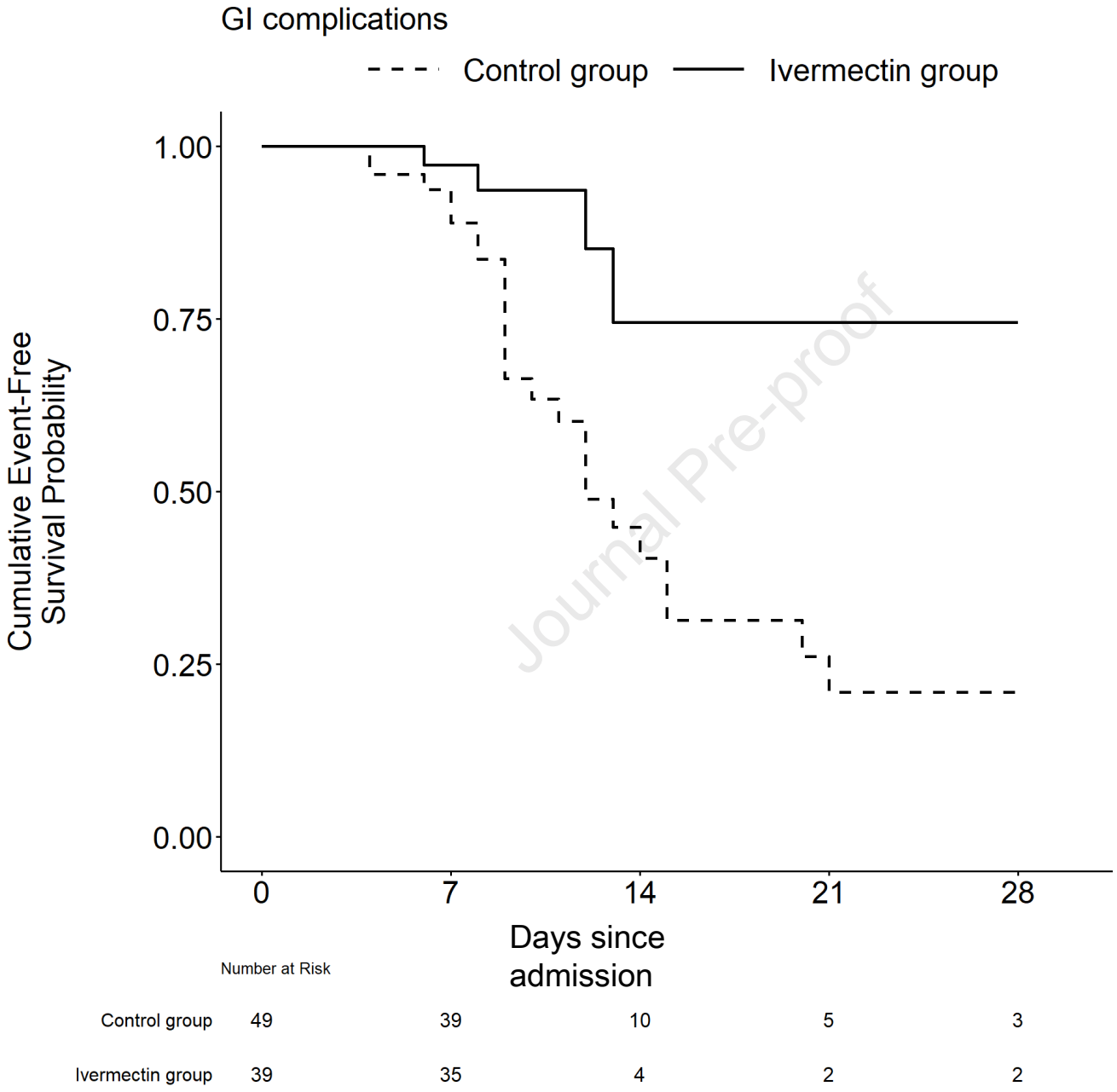

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Fig.1 (b)

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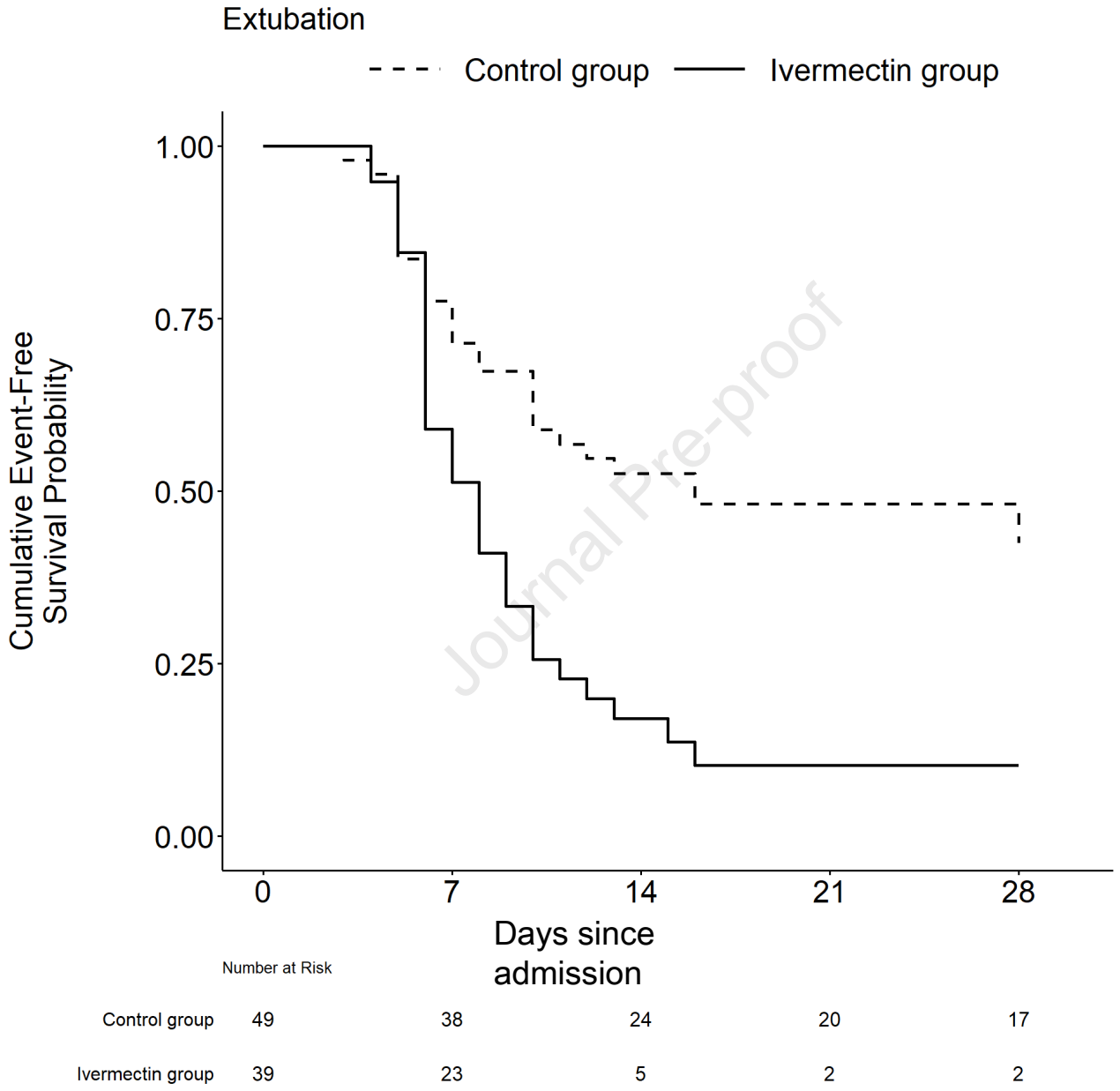

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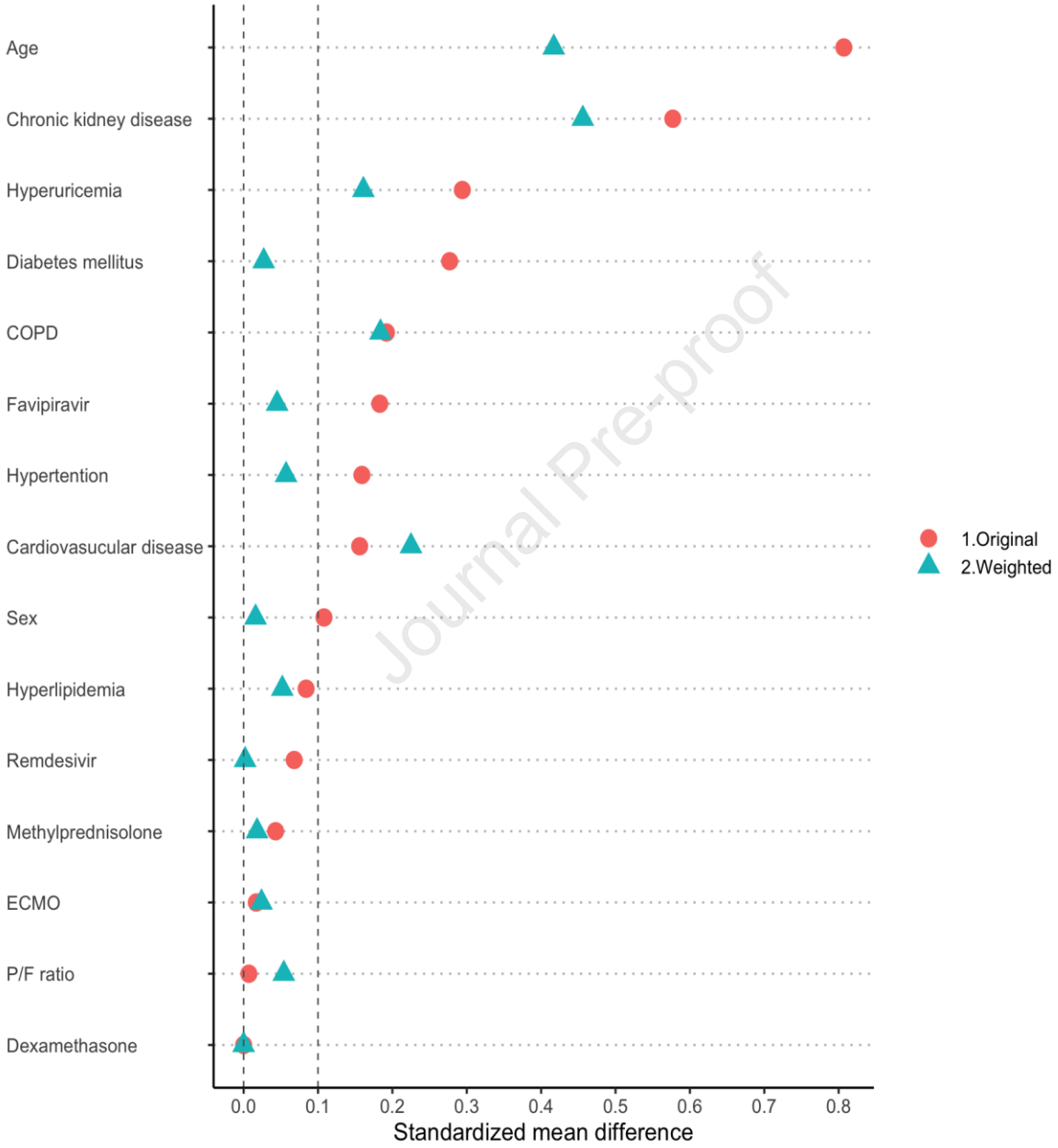
Fig.2

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